

Brief Report

Longitudinal Associations Between PM_{2.5} Chemical Components and Allostatic Load: An Individual Fixed-Effects Analysis in a Nationwide Panel Study

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Abstract

The longitudinal impact of fine particulate matter (PM_{2.5}) and its specific chemical drivers on multi-system physiological dysregulation, quantified by the allostatic load index (ALI), remains unclear. Leveraging panel data from 7421 middle-aged and older adults in the China Health and Retirement Longitudinal Study (CHARLS), we employed individual fixed-effects models—strictly controlling for time-invariant confounding—to evaluate the associations of PM_{2.5} and five components with ALI. Within-person increases in PM_{2.5} and all evaluated components significantly elevated ALI scores. Notably, secondary inorganic aerosols (SIAs: nitrate, ammonium, and sulfate) exerted the most pronounced effects, exhibiting J-shaped non-linear dose-response curves that suggest high-concentration exposures may overwhelm homeostatic buffering thresholds. This study provides the first longitudinal evidence identifying SIAs as the primary pollutants driving cumulative multi-system physiological decline in aging populations, offering critical support for component-specific air quality management.

Keywords: allostatic load; particulate matter components; secondary inorganic aerosols; individual fixed effects; physiological stress; aging; CHARLS

1. Introduction

As the global population ages, mitigating the environmental determinants of chronic physiological decline has become a paramount public health priority. PM_{2.5} is a well-established risk factor for specific age-related morbidities, including cardiovascular, respiratory, and metabolic diseases [1,2]. However, the aging process is rarely characterized by isolated organ failure; rather, it manifests as a cumulative, multi-system physiological dysregulation. To capture this systemic biological wear-and-tear, the concept of allostatic load has emerged as a critical pre-clinical biomarker [3]. Representing the cumulative burden of chronic stress mediated through the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system, the allostatic load index (ALI) integrates neuroendocrine, immune, metabolic, and cardiovascular biomarkers [4]. Clinically, elevated ALI is a powerful predictor of incident morbidity, functional decline, and all-cause mortality in older adults [5].

Despite the clinical significance of ALI, environmental epidemiological evidence linking ambient air pollution to allostatic overload remains conceptually and methodologically limited. First, current regulations and most epidemiological studies evaluate PM_{2.5} strictly based on its total mass concentration. Yet PM_{2.5} is a highly heterogeneous mixture of



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chemical constituents—such as carbonaceous fractions (black carbon, organic matter) and SIAs, each possessing distinct toxicological profiles [6,7]. The specific chemical drivers responsible for initiating and exacerbating multi-system physiological dysregulation in aging populations remain largely unknown.

The existing literature investigating air pollution and ALI is almost exclusively constrained to cross-sectional designs [8,9]. Two methodological traditions dominate this field, each with characteristic strengths and limitations. The first relies on cross-sectional multi-pollutant regression: such studies achieve large sample sizes and have reported positive associations between PM_{2.5} mass and ALI, but because exposure is compared between rather than within individuals, they remain vulnerable to unmeasured spatial and individual-level confounding—regional diet, healthcare access, and socioeconomic context are all correlated with both pollution and physiological risk [9]. The second characterizes exposure solely by PM_{2.5} total mass; this is regulation-relevant and simple to communicate, but it treats a chemically heterogeneous mixture as a single quantity and is therefore blind to component-specific toxicity. Against this backdrop, longitudinal within-person designs applied to speciated exposures, holding time-invariant confounders fixed while resolving the chemical drivers of risk, are needed but, to our knowledge, have not previously been reported for ALI.

To address these critical knowledge gaps, we conducted a nationwide longitudinal panel study leveraging data from the CHARLS cohort. By coupling high-resolution spatiotemporal pollution tracking with rich clinical biomarker data, we aimed to evaluate the associations between long-term exposure to PM_{2.5} and its five major chemical components with the trajectory of ALI in Chinese middle-aged and older adults. Crucially, we employed individual fixed-effects models, a rigorous approach that controls for time-invariant unmeasured confounding by relying exclusively on within-person temporal variation. Furthermore, we sought to characterize the non-linear exposure–response dynamics and the methodological challenges of isolating component-specific effects in multi-pollutant environments. To our knowledge, this is the first longitudinal, within-person study to identify secondary inorganic aerosols as the dominant chemical drivers of cumulative multi-system physiological dysregulation in an aging population, thereby advancing air-pollution risk assessment from total mass toward component-resolved evidence.

2. Methods

2.1. Study Population

This longitudinal study utilized data from the 2011 and 2015 waves of the CHARLS, a nationally representative cohort of Chinese adults. After excluding individuals missing valid clinical biomarker, exposure, or covariate data, we restricted the sample to participants with complete measurements in both waves—a strict requirement for individual fixed-effects modeling. The final analytical sample comprised 7421 participants, yielding 14,842 person-wave observations. The analysis was necessarily confined to the 2011 and 2015 waves because the complete venous blood-biomarker panel required to compute ALI was collected only in these two CHARLS waves; the 2013, 2018, and 2020 waves did not repeat the full assays, so no later wave permits construction of the index.

2.2. Allostatic Load Index (ALI)

To capture multi-system physiological dysregulation, we constructed the ALI from 14 clinical biomarkers spanning four physiological systems: cardiovascular (systolic and diastolic blood pressure); metabolic (body mass index, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, glycated hemoglobin [HbA1c], and fasting glucose); immune/inflammatory (C-reactive protein and hemoglobin); and renal (serum creatinine,

cystatin C, and blood urea nitrogen). For each biomarker, participants received 1 point if the measurement fell in the highest-risk quartile of the pooled (2011 and 2015 combined) sample distribution, the top quartile (≥ 75 th percentile) for all markers except HDL cholesterol, for which the bottom quartile (≤ 25 th percentile) was used, and 0 otherwise. A valid ALI required at least 8 non-missing biomarkers. The points were summed to yield a continuous ALI score ranging from 0 to 14.

2.3. Environmental Exposure Assessment

High-resolution monthly concentrations of PM_{2.5} total mass and five major chemical components, including sulfate (SO₄^{2−}), nitrate (NO₃[−]), ammonium (NH₄⁺), organic matter (OM), and black carbon (BC), were obtained from the Tracking Air Pollution in China (TAP) dataset. For each participant, we calculated the 1-year average concentration of each pollutant prior to the exact month of their clinical blood draw, matched to their residential city.

2.4. Statistical Analysis

We employed individual (two-way) fixed-effects linear regression to evaluate the longitudinal associations between air pollutants and ALI. The estimating equation was $ALI_{it} = \beta \cdot Exposure_{it} + \gamma \cdot CookingFuel_{it} + \delta \cdot MaritalStatus_{it} + \alpha_i + \lambda_t + \varepsilon_{it}$, where i indexes participants and t indexes wave (2011 or 2015). The individual fixed effect (α_i) absorbs all time-invariant characteristics of each participant (e.g., sex, educational attainment, genetic background, stable dietary habits, and baseline residential environment); the wave fixed effect (λ_t) absorbs nationwide secular trends and, being deterministic, chronological age. $Exposure_{it}$ is the 1-year mean concentration of a given pollutant PM_{2.5} scaled per 10 $\mu\text{g}/\text{m}^3$; each chemical component per interquartile range, and $CookingFuel$ and $MaritalStatus$ are the two time-varying covariates retained after fixed-effects absorption; time-invariant covariates such as sex and ever-smoking status were not entered separately because they are absorbed by the fixed effects. Because each participant contributes two repeated observations, within-person correlation was addressed in two complementary ways: identification relies exclusively on within-person change (each participant serves as their own control, so with two waves the estimator is algebraically equivalent to a first-difference model), and all standard errors were clustered at the individual level. Restricted cubic splines (RCS) with three knots (10th, 50th, and 90th percentiles) were used to explore non-linear exposure–response dynamics. Two-pollutant models were constructed to examine the independent effects of specific components by additionally adjusting for concurrent PM_{2.5} mass. Given the within-person longitudinal design, high collinearity between PM_{2.5} and its secondary inorganic components could inflate variance and yield non-significant estimates; such results were interpreted cautiously. All analyses were performed in Python 3.10 using statsmodels 0.14 and linearmodels 7.0. Two-sided $p < 0.05$ was considered statistically significant.

3. Results and Discussion

3.1. Study Population and Baseline Characteristics

The primary analytical sample comprised 7421 participants who completed clinical biomarker assessments in both the 2011 and 2015 waves, contributing a total of 14,842 person-wave observations for the individual fixed-effects models. At baseline, the mean age of this panel subset was 59.2 ± 9.8 years, and 53.5% were female. The overall mean Allostatic Load Index (ALI) score was 3.6 ± 2.2 . Baseline demographic and behavioral characteristics stratified by ALI tertiles are detailed in Table 1. The longitudinal within-person variations observed in both the clinical biomarkers and ambient air

pollution exposures over the study period provided sufficient identifying variation for the fixed-effects estimation.

Table 1. Baseline characteristics of the primary panel cohort stratified by Allostatic Load Index (ALI) score categories.

Group	Low	Medium	High	Overall
N	4096	3865	3613	11,574
ALI score	1.3 ± 0.8	3.5 ± 0.5	6.2 ± 1.4	3.6 ± 2.2
Age (years)	56.8 ± 9.2	59.7 ± 9.8	61.2 ± 9.8	59.2 ± 9.8
Female, <i>n</i> (%)	2567 (62.7%)	1978 (51.2%)	1649 (45.6%)	6194 (53.5%)
Age ≥ 65, <i>n</i> (%)	784 (19.1%)	1126 (29.1%)	1245 (34.5%)	3155 (27.3%)
Ever smoker, <i>n</i> (%)	1285 (31.4%)	1592 (41.2%)	1613 (44.6%)	4490 (38.8%)
Dirty fuel, <i>n</i> (%)	2308 (56.3%)	2242 (58.0%)	1942 (53.8%)	6492 (56.1%)
Rural, <i>n</i> (%)	2728 (66.6%)	2501 (64.7%)	2101 (58.2%)	7330 (63.3%)
Married, <i>n</i> (%)	3700 (90.3%)	3356 (86.8%)	3122 (86.4%)	10,178 (87.9%)
PM _{2.5} 3 year (µg/m ³)	57.5 ± 23.6	57.5 ± 24.0	57.1 ± 24.7	57.4 ± 24.1
SO ₄ ^{2−} 3 year (µg/m ³)	11.1 ± 4.3	11.1 ± 4.3	11.0 ± 4.4	11.0 ± 4.3
NO ₃ [−] 3 year (µg/m ³)	11.7 ± 5.8	11.7 ± 5.9	11.6 ± 6.0	11.7 ± 5.9
NH ₄ ⁺ 3 year (µg/m ³)	8.5 ± 3.7	8.5 ± 3.7	8.4 ± 3.8	8.5 ± 3.7
OM 3 year (µg/m ³)	14.1 ± 5.2	14.1 ± 5.3	14.0 ± 5.5	14.0 ± 5.3
BC 3 year (µg/m ³)	3.0 ± 1.0	3.0 ± 1.0	3.0 ± 1.0	3.0 ± 1.0

Data are presented as mean ± standard deviation for continuous variables and *n* (%) for categorical variables. *p*-values were calculated using Analysis of Variance (ANOVA) for continuous variables and Pearson's chi-square test for categorical variables across ALI score categories. Abbreviations: ALI, allostatic load index.

3.2. Longitudinal Associations

After rigorously controlling for time-invariant spatial and individual confounding through individual fixed-effects models, within-person increases in PM_{2.5} and all five of its major chemical components were significantly associated with elevated ALI scores (Figure 1).

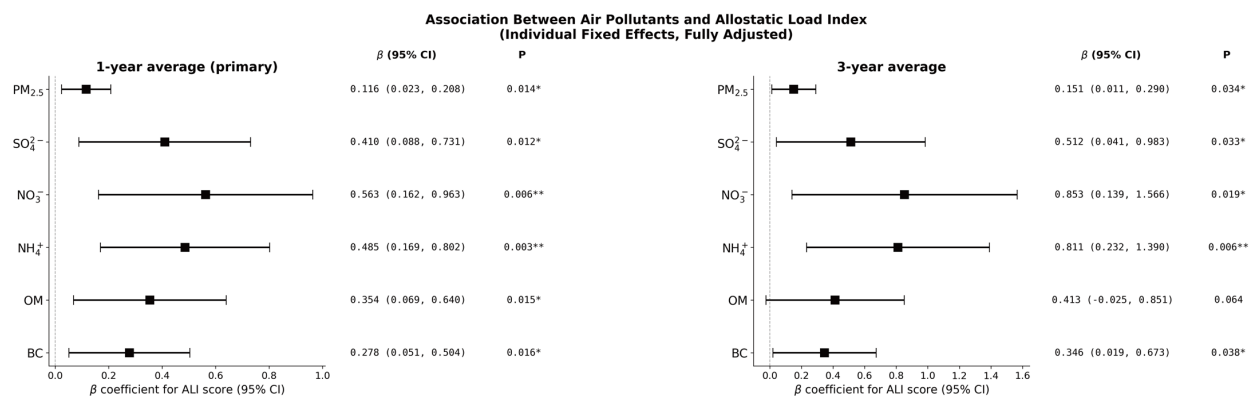


Figure 1. Longitudinal associations between ambient air pollutants and the Allostatic Load Index (ALI). Forest plot displaying the independent effect estimates (β coefficients) and 95% confidence intervals (CIs) for the within-person change in the continuous ALI score per 10 µg/m³ increase in PM_{2.5} total mass and per interquartile range (IQR) increase in each chemical component (NO₃[−], NH₄⁺, SO₄^{2−}, organic matter [OM], and black carbon [BC]). The left panel shows the primary 1-year average exposure and the right panel the 3-year average exposure (sensitivity analysis). All estimates were derived from single-pollutant individual fixed-effects models, strictly controlling for time-invariant confounding. Abbreviations: PM_{2.5}, fine particulate matter; BC, black carbon; OM, organic matter; NH₄⁺, ammonium; NO₃[−], nitrate; SO₄^{2−}, sulfate., ** *p* < 0.01, * *p* < 0.05.

Notably, SIAs exerted the strongest pro-dysregulatory effects. Each interquartile range (IQR) increase in NO₃[−], NH₄⁺, and SO₄^{2−} corresponded to ALI increases of 0.563, 0.485, and 0.410, respectively. Carbonaceous components (organic matter and black carbon) and

total PM_{2.5} mass exhibited significant, yet comparatively weaker, positive associations. Subgroup analyses indicated that these associations remained consistent across baseline demographic and behavioral strata (sex, age, residence, smoking, and cooking fuel), with no significant effect modification for ammonium (Figure 2); the full component $\times$ stratum matrix for all six pollutants is provided in Table 2.

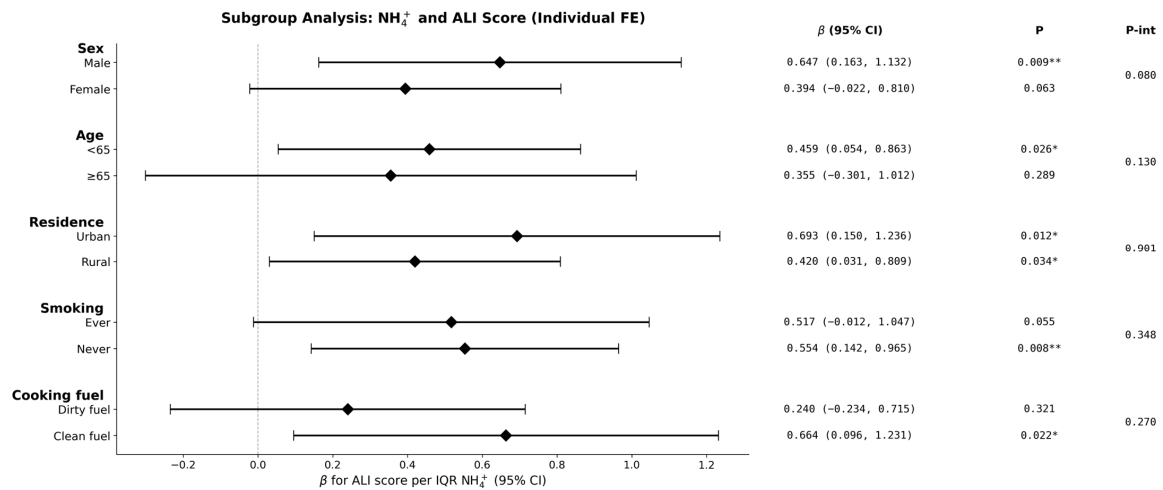


Figure 2. Subgroup analyses for the association between ammonium (NH₄⁺) exposure and ALI. The forest plot presents the estimated changes (β) and 95% confidence intervals (CIs) in the continuous ALI score per interquartile range (IQR) increase in 1-year average NH₄⁺ exposure, stratified by pre-specified baseline demographic and behavioral characteristics. P-values for interaction (P-int) were calculated from multiplicative interaction terms (exposure $\times$ subgroup indicator) in the full sample. To preserve statistical power within the smaller strata, each stratified model included individual and wave fixed effects only (Model I), without additional covariates; the individual fixed effect inherently controls for all time-invariant confounding, ** $p < 0.01$, * $p < 0.05$.

Biologically, the pronounced impact of SIAs on allostatic load is consistent with their high water solubility and oxidative potential. Unlike larger or less soluble particulate matter, SIAs can readily cross the alveolar epithelium and enter the systemic circulation, directly inducing widespread oxidative stress and systemic inflammation [10]. This chronic inflammatory state continuously hyperactivates the HPA axis and the sympathetic nervous system [11]. The ensuing persistent release of stress hormones ultimately disrupts neuroendocrine, metabolic, and cardiovascular homeostasis, manifesting clinically as a progressive elevation in the ALI score.

Table 2. Subgroup analyses of the associations between 1-year average air pollutant exposures and the Allostatic Load Index (ALI), across all six pollutants and five pre-specified strata (sex, age, residence, smoking, and cooking fuel). Estimates are the change in ALI score per 10 $\mu\text{g}/\text{m}^3$ (PM_{2.5}) or per interquartile range (each chemical component), from individual and wave fixed-effects models fitted within each stratum to preserve statistical power. β , regression coefficient; CI, confidence interval.

Pollutant (Unit)	Subgroup	Stratum	β (95% CI)	p-Value
PM _{2.5} (per 10 $\mu\text{g}/\text{m}^3$)	Sex	Male	0.156 (0.014, 0.298)	0.031
	Sex	Female	0.095 (-0.026, 0.216)	0.125
	Age	<65	0.118 (0.000, 0.236)	0.049
	Age	≥65	0.040 (-0.153, 0.234)	0.682
	Residence	Urban	0.152 (-0.006, 0.311)	0.060
	Residence	Rural	0.111 (-0.003, 0.225)	0.055
	Smoking	Ever	0.111 (-0.045, 0.267)	0.162
	Smoking	Never	0.137 (0.018, 0.256)	0.024
	Cooking fuel	Dirty	0.054 (-0.082, 0.190)	0.439
	Cooking fuel	Clean	0.176 (0.009, 0.343)	0.039

Table 2. Cont.

Pollutant (Unit)	Subgroup	Stratum	β (95% CI)	<i>p</i> -Value
SO ₄ ²⁻ (per IQR)	Sex	Male	0.583 (0.092, 1.075)	0.020
	Sex	Female	0.306 (−0.117, 0.730)	0.156
	Age	<65	0.413 (0.001, 0.825)	0.050
	Age	≥65	0.198 (−0.461, 0.858)	0.556
	Residence	Urban	0.564 (0.024, 1.105)	0.041
	Residence	Rural	0.373 (−0.027, 0.774)	0.068
	Smoking	Ever	0.433 (−0.106, 0.971)	0.115
	Smoking	Never	0.468 (0.050, 0.886)	0.028
	Cooking fuel	Dirty	0.173 (−0.307, 0.653)	0.481
	Cooking fuel	Clean	0.621 (0.046, 1.195)	0.034
NO ₃ ⁻ (per IQR)	Sex	Male	0.714 (0.100, 1.328)	0.023
	Sex	Female	0.496 (−0.031, 1.022)	0.065
	Age	<65	0.523 (0.015, 1.031)	0.044
	Age	≥65	0.394 (−0.452, 1.241)	0.361
	Residence	Urban	0.799 (0.109, 1.489)	0.023
	Residence	Rural	0.496 (0.005, 0.987)	0.048
	Smoking	Ever	0.552 (−0.118, 1.222)	0.107
	Smoking	Never	0.687 (0.167, 1.207)	0.010
	Cooking fuel	Dirty	0.288 (−0.321, 0.897)	0.354
	Cooking fuel	Clean	0.726 (0.015, 1.436)	0.045
NH ₄ ⁺ (per IQR)	Sex	Male	0.647 (0.163, 1.132)	0.009
	Sex	Female	0.394 (−0.022, 0.810)	0.063
	Age	<65	0.459 (0.054, 0.863)	0.026
	Age	≥65	0.355 (−0.301, 1.012)	0.289
	Residence	Urban	0.693 (0.150, 1.236)	0.012
	Residence	Rural	0.420 (0.031, 0.809)	0.034
	Smoking	Ever	0.517 (−0.012, 1.047)	0.055
	Smoking	Never	0.554 (0.142, 0.965)	0.008
	Cooking fuel	Dirty	0.240 (−0.234, 0.715)	0.321
	Cooking fuel	Clean	0.664 (0.096, 1.231)	0.022
OM (per IQR)	Sex	Male	0.532 (0.093, 0.972)	0.018
	Sex	Female	0.231 (−0.143, 0.606)	0.226
	Age	<65	0.374 (0.004, 0.744)	0.048
	Age	≥65	0.119 (−0.461, 0.698)	0.688
	Residence	Urban	0.524 (−0.004, 1.052)	0.052
	Residence	Rural	0.310 (−0.031, 0.650)	0.075
	Smoking	Ever	0.414 (−0.066, 0.894)	0.091
	Smoking	Never	0.362 (−0.007, 0.732)	0.054
	Cooking fuel	Dirty	0.137 (−0.261, 0.534)	0.500
	Cooking fuel	Clean	0.562 (0.021, 1.102)	0.042
BC (per IQR)	Sex	Male	0.442 (0.095, 0.790)	0.012
	Sex	Female	0.156 (−0.141, 0.454)	0.303
	Age	<65	0.314 (0.020, 0.608)	0.036
	Age	≥65	0.084 (−0.365, 0.533)	0.713
	Residence	Urban	0.415 (0.015, 0.814)	0.042
	Residence	Rural	0.235 (−0.041, 0.510)	0.095
	Smoking	Ever	0.328 (−0.051, 0.707)	0.090
	Smoking	Never	0.272 (−0.021, 0.565)	0.069
	Cooking fuel	Dirty	0.093 (−0.230, 0.415)	0.573
	Cooking fuel	Clean	0.472 (0.062, 0.882)	0.024

Estimates are the change in ALI score per 10 µg/m³ (PM_{2.5}) or per interquartile range (chemical components), derived from individual and wave fixed-effects models (Model I) within each stratum to preserve statistical power; the individual fixed effect controls for all time-invariant confounding. β , regression coefficient; CI, confidence interval.

3.3. Non-Linear Dynamics

Restricted cubic spline analyses revealed distinct J-shaped, non-linear dose-response relationships between SIAs and ALI (Figure 3). The curves remained relatively flat at lower exposure levels but exhibited steep, monotonic increases beyond specific thresholds. This pattern suggests that while local antioxidant defenses and immune buffering may maintain homeostasis under low-dose exposures, these compensatory mechanisms are ultimately exceeded at higher concentrations, triggering a disproportionate systemic inflammatory response.

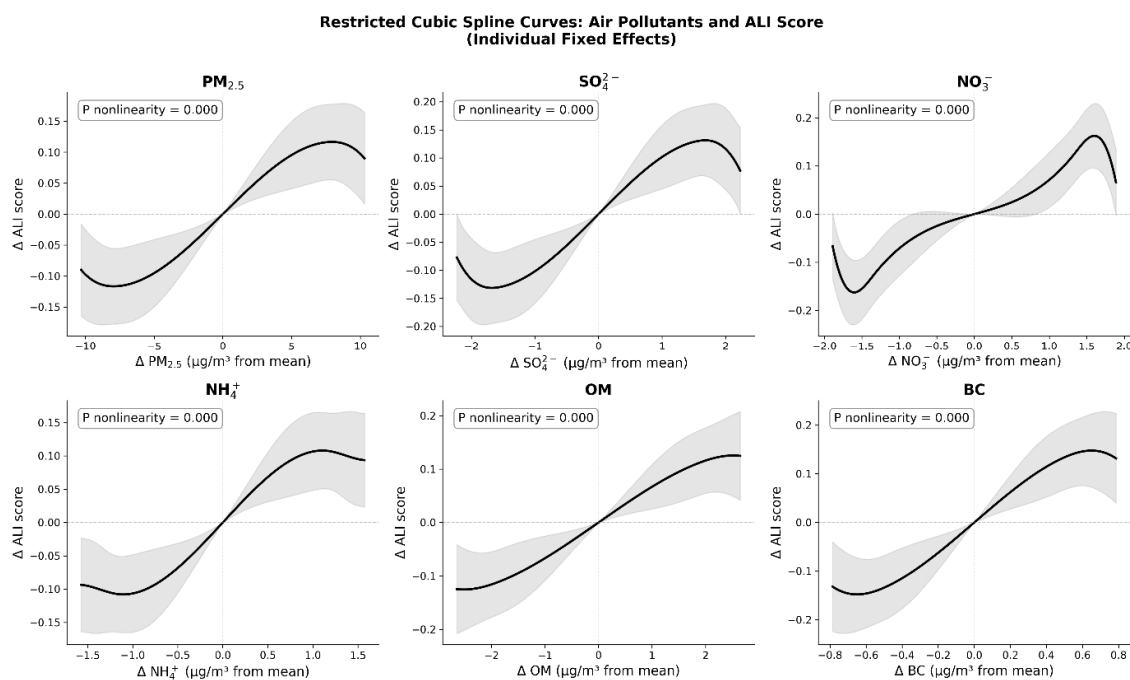


Figure 3. Restricted cubic spline (RCS) curves illustrating the non-linear exposure–response relationships between ambient air pollutants and the Allostatic Load Index (ALI). The curves model the longitudinal within-person associations between 1-year average exposures to PM_{2.5} and its chemical components and ALI. Splines were fitted with three knots placed at the 10th, 50th, and 90th percentiles of the respective pollutant distributions in the individual fixed-effects models. The solid lines represent the point estimates of the change in ALI score, and the shaded areas denote the 95% confidence intervals. The secondary inorganic aerosols (SIAs) exhibit distinct J-shaped non-linear thresholds.

In two-pollutant models adjusting for concurrent total PM_{2.5} mass (Table 3), the independent effect estimates for most components were substantially attenuated and lost statistical significance; ammonium (NH₄⁺) was the exception, remaining significant ($\beta = 0.976$, $p = 0.037$). Diagnostic evaluation revealed extreme multicollinearity between PM_{2.5} and its secondary inorganic components: within-person variance inflation factors for the 1-year exposures ranged from 69 to 195 (all far exceeding the conventional threshold of 10), consistent with Spearman correlations as high as 0.98. Because the individual fixed-effects specification discards cross-sectional spatial variation and relies exclusively on within-person temporal changes, the collinearity between PM_{2.5} mass and its major components over time becomes mathematically prohibitive. Consequently, this attenuation reflects a fundamental statistical limitation of applying multi-pollutant adjustments within strict temporal-variance frameworks, rather than implying a genuine absence of independent component effects.

Table 3. Longitudinal associations between ambient air pollutants and the Allostatic Load Index (ALI) in single- and two-pollutant individual fixed-effects models.

Exposure	Model Type	Adjusted for	β (95% CI)	p-Value
PM _{2.5}	Single	None	0.116 (0.023, 0.208)	0.014
SO ₄ ^{2−}	Single	None	0.410 (0.088, 0.731)	0.012
NO ₃ [−]	Single	None	0.563 (0.162, 0.963)	0.006
NH ₄ ⁺	Single	None	0.485 (0.169, 0.802)	0.003
OM	Single	None	0.354 (0.069, 0.640)	0.015
BC	Single	None	0.278 (0.051, 0.504)	0.016
PM _{2.5}	Two-pollutant	SO ₄ ^{2−}	0.006 (−0.523, 0.536)	0.982
SO ₄ ^{2−}	Two-pollutant	PM _{2.5}	0.389 (−1.455, 2.233)	0.679
PM _{2.5}	Two-pollutant	NO ₃ [−]	−0.034 (−0.282, 0.214)	0.787
NO ₃ [−]	Two-pollutant	PM _{2.5}	0.701 (−0.374, 1.776)	0.201
PM _{2.5}	Two-pollutant	NH ₄ ⁺	−0.152 (−0.419, 0.116)	0.267
NH ₄ ⁺	Two-pollutant	PM _{2.5}	0.976 (0.058, 1.894)	0.037
PM _{2.5}	Two-pollutant	OM	0.066 (−0.215, 0.346)	0.646
OM	Two-pollutant	PM _{2.5}	0.162 (−0.705, 1.030)	0.714
PM _{2.5}	Two-pollutant	BC	0.071 (−0.155, 0.298)	0.536
BC	Two-pollutant	PM _{2.5}	0.118 (−0.436, 0.672)	0.675

Data are presented as effect estimates (β coefficients) and 95% confidence intervals (CIs) representing the change in ALI score per interquartile range (IQR) increase in pollutant concentrations. Estimates were derived from individual fixed-effects regression models adjusting for time-varying covariates. Abbreviations: ALI, allostatic load index; CI, confidence interval; IQR, interquartile range; PM_{2.5}, fine particulate matter with an aerodynamic diameter $\leq 2.5 \mu\text{m}$; SO₄^{2−}, sulfate; NO₃[−], nitrate; NH₄⁺, ammonium; OM, organic matter; BC, black carbon.

3.4. Limitations

This study extends the current understanding of pre-clinical environmental health by utilizing a longitudinal, within-person design. Previous epidemiological investigations linking air pollution to ALI have relied almost exclusively on cross-sectional data, which are inherently vulnerable to unmeasured spatial confounders such as genetic predisposition, long-term dietary habits, and local healthcare accessibility. By isolating temporal effects from these time-invariant confounders, our fixed-effects approach provides more robust causal evidence that long-term SIA exposure acts as a chronic environmental stressor.

Several limitations should be noted. First, the availability of only two waves of comprehensive clinical biomarker data precluded the modeling of complex, long-term trajectories of physiological decline. Second, because the CHARLS cohort comprises Chinese middle-aged and older adults exposed to relatively high ambient pollution levels, the generalizability of the observed non-linear thresholds to populations in low-pollution settings requires further empirical validation. Third, CHARLS enrolls adults aged 45 years and older, so our estimates apply to middle-aged and older adults and cannot be extrapolated to younger populations; within the observed range, effect modification by age was not statistically significant (P-interaction = 0.130 for the <65 vs. ≥ 65 years contrast), but whether younger adults with greater physiological reserve exhibit smaller or delayed responses warrants dedicated cohorts. Finally, because ALI can be constructed only for the two blood-collection waves, the study window (2011–2015) is fixed by data availability rather than chosen, and updated assessments will require future biomarker waves.

3.5. Generalizability and Transferability

The estimating framework used here, two-way fixed effects applied to repeated, spatially resolved speciated exposures, is portable to any panel cohort with at least two biomarker waves and extends directly to other pollutants (e.g., ozone, NO₂) or exposure metrics. Three caveats govern such transfer. First, because the exposure–response relationship is non-linear, populations with different baseline exposure ranges occupy

different regions of the curve, so absolute effect sizes are not directly transferable across settings even when the qualitative pattern holds. Second, fixed-effects identification requires genuine within-person change in exposure over time and is therefore less informative where pollution levels are spatially and temporally static. Third, because ALI composition and biomarker thresholds vary across populations, cohort-specific percentile scoring and, where more than two waves are available, mixed models with individual random effects would improve comparability. These considerations define a concrete agenda for replicating and generalizing our findings across other countries and age ranges.

4. Conclusions

Within-person longitudinal increases in PM_{2.5} and its specific chemical components are significantly associated with exacerbated multi-system physiological dysregulation in middle-aged and older adults. This study makes three contributions: it provides longitudinal, within-person evidence that overcomes the time-invariant confounding intrinsic to prior cross-sectional work; it resolves the chemical mixture, identifying secondary inorganic aerosols (nitrate, ammonium, and sulfate) as the dominant drivers rather than PM_{2.5} total mass alone; and it demonstrates a non-linear, threshold-like exposure–response pattern consistent with the exhaustion of homeostatic buffering at higher exposures. Together, these findings support a paradigm shift toward component-aware environmental risk stratification and underscore the need to prioritize control of secondary inorganic aerosol precursor emissions to mitigate the cumulative physiological burden of population aging.

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Institutional Review Board Statement: This study used publicly available, de-identified secondary data from the China Health and Retirement Longitudinal Study (CHARLS). The original CHARLS study was approved by the Biomedical Ethics Review Committee of Peking University/Institutional Review Board of Peking University (approval No. IRB00001052-11015; and, where applicable, approval No. IRB00001052-11014 for biomarker collection). As the present study involved only secondary analysis of de-identified data, additional ethical approval was not required.

Informed Consent Statement: Written informed consent was obtained from all participants at the time of their participation in the original CHARLS study. No additional informed consent was required for the present secondary analysis of de-identified data.

Data Availability Statement: CHARLS data are available through the CHARLS repository, subject to the database's access procedures.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

ALI	Allostatic load index
PM _{2.5}	fine particulate matter with aerodynamic diameter $\leq 2.5 \mu\text{m}$
SIA	secondary inorganic aerosol
SO ₄ ^{2−}	sulfate
NO ₃ [−]	nitrate
NH ₄ ⁺	ammonium
OM	organic matter
BC	black carbon
FE	fixed effects
IQR	interquartile range
RCS	restricted cubic spline

CHARLS	China Health and Retirement Longitudinal Study
TAP	Tracking Air Pollution in China
GADM	Database of Global Administrative Areas
CRP	C-reactive protein
HbA1c	glycated hemoglobin
BUN	blood urea nitrogen
HDL-C	high-density lipoprotein cholesterol
LDL-C	low-density lipoprotein cholesterol
HPA	Hypothalamic–pituitary–adrenal

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